Form PTO 1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER P32286
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5) 10/019355
INTERNATIONAL APPLICATION NO. PCT/GB00/01521	INTERNATIONAL FILING DATE 19 April 2000	PRIORITY DATE CLAIMED 20 April 1999
TITLE OF INVENTION NOVEL PHARMACEUTICAL		
APPLICANT(S) FOR DO/EO/US Paul David James BLACKLER, Robert Gordon GILES and Michael John SASSE		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1 [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.

2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.

3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).

4. [x] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.

5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [x] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).

6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).

7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.

8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S. C. 371(c)(3)).

9. [ ] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).

10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [x] An Information Disclosure Statement under 37 C.F.R. 1.97 and 1.98; and Form PTO-1449.

12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 C.F.R. 3.28 and 3.31 is included.

13. [x] A FIRST preliminary amendment.

14. [ ] A SECOND or SUBSEQUENT preliminary amendment.

15. [x] Please amend the specification by inserting before the first line the sentence: This is a 371 of International Application PCT/GB00/01521, filed 19 April 2000.

16. [ ] A substitute specification.

17. [ ] A change of power of attorney and/or address letter.

18. [x] An Abstract on a separate sheet of paper.

19. [ ] Other items or information:

US APPLICATION NO. (if known see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEYS DOCKET NO.
10/019555	PCT/GB00/01521	P32286

20. [X] The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 C.F.R. 1.492(a)(1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**	**$890.00**	
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) **$710.00**		
No International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither International Preliminary Examination Fee (37 CFR 1.492) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$1,040.00**		
International Preliminary Examination Fee paid to USPTO (37 CFR 1.492) and all claims satisfied provisions of PCT Article 33(2)-(4).....**$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0.00**	

Claims	Number Filed	Number Extra	Rate		
Total claims	**9 - 20 =**	**0**	**0 x $18.00**	**$0.00**	
Independent claims	**3 - 3 =**	**0**	**0 x $84.00**	**$0.00**	
Multiple dependent claims (if applicable)			**+ $280.00**	**$0.00**	
TOTAL OF ABOVE CALCULATIONS =				**$890.00**	
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)) +				**$**	
TOTAL NATIONAL FEE =				**$890.00**	
				Amount to be refunded	**$**
				charged	**$**

a. ☐ A check in the amount of $____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 19-2570 in the amount of **$890.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-2570 . A duplicate copy of this sheet is enclosed.

d. ☒ General Authorization to charge any and all fees under 37 CFR 1.16 or 1.17, including petitions for extension of time relating to this application (37 CFR 1.136 (a)(3)).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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33,797
REGISTRATION NO.

"EXPRESS MAIL CERTIFICATE"
"EXPRESS MAIL" MAILING LABEL NUMBER EV000521179US
DATE OF DEPOSIT 19 OCTOBER 2001

Attorney Docket No. P32286

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/01521	19 April 2000	20 April 1999

TITLE OF INVENTION
NOVEL PHARMACEUTICAL

APPLICANT(S) FOR DO/US
Paul David James BLACKLER, Robert Gordon GILES and Michael John SASSE

PRELIMINARY AMENDMENT

Preliminary to the examination of this application, Applicants respectfully request amendment of the above-identified application as follows:

In the Specification:

Kindly add the Abstract enclosed herewith on a separate sheet, at the end.

In the Claims:

Please cancel claims 9-11.

Please amend claims 1, 3-6, and 12 as follows:

1. (Amended) 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate comprising:

(ii) provides an infrared spectrum containing peaks at 3392, 2739, 1751, 1325 and 713 cm^{-1}; and/or

(ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at 9.1, 12.0, 15.7, 16.3 and 19.8 °2θ.

3. (Amended) A hydrate according to claim 1, which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure II.

4. (Amended) A hydrate according to claim 1, in isolated form.

5. (Amended) A hydrate according to claim 1, in pure form.

6. (Amended) A hydrate according to claim 1, in crystalline form.

Int'l App. No.: PCT/GB00/01521
Int'l Filing Date: 19 April 2000

12. (Amended) A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of hydrate according to claim 1 to a human or non-human mammal in need thereof.

REMARKS

The above-identified application is being entered into the National Phase from PCT application No. PCT/GB00/01521.

Applicants have amended the claims to put them in conformity with U.S. practice. Attached hereto is a marked up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made."**

No new matter has been introduced.

Respectfully submitted,

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Int'l App. No.: PCT/GB00/01521
Int'l Filing Date: 19 April 2000

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

An abstract has been added.

In the Claims:

Claims 9-11 have been canceled.

1. (Amended) 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate [characterized in that it] comprising:

(ii) provides an infrared spectrum containing peaks at 3392, 2739, 1751, 1325 and 713 cm^{-1}; and/or

(ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at 9.1, 12.0, 15.7, 16.3 and 19.8 °2θ.

3. (Amended) A hydrate according to claim 1 [or claim 2], which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure II.

4. (Amended) A hydrate according to [any one of] claim[s] 1 [to 3], in isolated form.

5. (Amended) A hydrate according to [any one of] claim[s] 1 [to 4], in pure form.

6. (Amended) A hydrate according to [any one of] claim[s] 1 [to 5], in crystalline form.

12. (Amended) A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of hydrate according to claim 1 to a human or non-human mammal in need thereof.

"EXPRESS MAIL CERTIFICATE"
"EXPRESS MAIL" MAILING LABEL NUMBER EV000522877US
DATE OF DEPOSIT MARCH 22, 2002.

Attorney's Docket No. P32286

INTERNATIONAL APP. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB00/01521	19 April 2000	20 April 1999

TITLE OF INVENTION
NOVEL PHARMACEUTICAL

APPLICANT(S) FOR DO/US
Paul David James BLACKLER, Robert Gordon GILES and Michael John SASSE

SUPPLEMENTARY PRELIMINARY AMENDMENT UNDER 37 C.F.R. §1.111

Preliminary to the examination of this application, Applicants respectfully request amendment of the above-identified application as follows:

In the Title:

Please amend the title to read:

-- THIAZOLIDINEDIONE DERIVATIVE AND ITS USE AS ANTIDIABETIC --

REMARKS

For clarification, the title has been amended. No new matter has been added.

Attached hereto is a marked up version of the change made to the title by the current amendment. The attached page is captioned **"Version with Markings to Show Changes Made."**

Respectfully submitted,

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Int'l App. No.: PCT/GB00/01521
Int'l Filing Date: 19 April 2000

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Title:

[NOVEL PHARMACEUTICAL] THIAZOLIDINEDIONE DERIVATIVE AS ITS USE AS ANTIDIABETIC

10/019355
PCT/GB00/01521
Rec'd PCT/PTO 19 OCT 2001

NOVEL PHARMACEUTICAL

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

European Patent Application, Publication Number 0,306,228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of example 30 of EP 0,306,228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter also referred to as "Compound I").

International Patent Application, Publication Number WO94/05659 discloses certain salts of the compounds of EP 0,306,228 and in particular the maleic acid salt.

International Patent Applications, Publication Numbers WO99/31093, WO99/31094 and WO99/31095 each disclose distinct hydrates of Compound (I).

It has now been discovered that Compound (I) exists in the form of a novel hydrochloride salt which is dihydrated. This novel hydrochloride salt dihydrate (hereinafter also referred to as "Hydrochloride Hydrate") is particularly suitable for bulk preparation and handling. The novel form can be prepared by an efficient, economic and reproducible process particularly suited to large-scale preparation.

The novel Hydrochloride Hydrate also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate characterised in that it:

(i) provides an infrared spectrum containing peaks at 3392, 2739, 1751, 1325 and 713 cm^{-1}; and/or

(ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at 9.1, 12.0, 15.7, 16.3 and 19.8 °2θ.

In one favoured aspect, Hydrochloride Hydrate provides an infra red spectrum substantially in accordance with Figure I.

In one favoured aspect, Hydrochloride Hydrate provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure II.

The Hydrochloride Hydrate may exist in certain dehydrated forms which reversibly convert to the Hydrochloride Hydrate when contacted with water, either in liquid or vapour form. The present invention encompasses all such reversibly rehydratable forms of the Hydrochloride Hydrate. Preferably, there is provided the hydrated form as characterised above.

The present invention encompasses Hydrochloride Hydrate isolated in pure form or when admixed with other materials.

Thus in one aspect there is provided Hydrochloride Hydrate in isolated form.

In a further aspect there is provided Hydrochloride Hydrate in pure form.

In yet a further aspect there is provided Hydrochloride Hydrate in crystalline form.

The invention also provides a process for preparing Hydrochloride Hydrate, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) is treated with aqueous hydrochloric acid and thereafter the required compound is recovered.

Suitably, the aqueous hydrochloric acid is formed by admixing concentrated hydrochloric acid and water or an appropriate organic solvent, such as denatured ethanol or propan-2-ol, or mixtures thereof.

Suitably the reaction is carried out at ambient temperature but any convenient temperature may be employed which provides the required product.

In one aspect the Hydrochloride Hydrate is prepared by:

(i) treating 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione in aqueous propan-2-ol with aqueous hydrochloric acid at an elevated temperature, such as a temperature in the range of from 60 °C to 80 °C, suitably 65 °C to 75 °C, for example 75°C;

(ii) the solution is cooled to ambient temperature, for example 25°C;

(iii) the solution is seeded with the Hydrochloride Hydrate, preferably the reaction temperature is further reduced to a temperature in the range of from 0 to 5°C to complete crystallisation.

In the above mentioned process the total amount of water in the reaction mixture is preferably in the range of from 15% to 50%w/v, suitably 25% to 40%w/v, for example 27%w/v.

It will be appreciated that in the above mentioned processes hydrochloric acid may be replaced by any suitable source of hydrochloride ions, providing the amount of water in the reaction is suitable for formation of the of Hydrochloride Hydrate. The suitable amount of water is generally at least two molar equivalents and generally an excess over this, for example an amount equivalent to that used in the above mentioned processes.

Recovery of the required compound generally comprises crystallisation from an appropriate solvent such as water or aqueous denatured ethanol.

Crystallisation is generally carried out at low to ambient temperature, such as in the range of from 0 to 30°C for example 25°C; alternatively crystallisation may be initiated at an elevated temperature, such as in the range of from 30°C and 60°C for

example 50°C, and then completed by allowing the temperature of the solvent to cool to ambient or low temperature, such as in the range of from 0 to 30°C for example 25°C. The crystallisation can be initiated by seeding with crystals of Hydrochloride Hydrate but this is not essential.

Compound (I) is prepared according to known procedures, such as those disclosed in EP 0,306,228 and WO94/05659. The disclosures of EP 0,306,228 and WO94/05659 are incorporated herein by reference.

When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes.

Diabetes mellitus preferably means Type II diabetes mellitus.

Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating , such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

The complications of conditions associated with diabetes mellitus encompassed herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly Hydrochloride Hydrate for use as an active therapeutic substance.

More particularly, the present invention provides Hydrochloride Hydrate for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

Hydrochloride Hydrate may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. The formulation of Hydrochloride Hydrate is generally as disclosed for Compound (I) in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising Hydrochloride Hydrate and a pharmaceutically acceptable carrier therefor.

Hydrochloride Hydrate is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending

on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of Hydrate to a human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In addition, the Hydrochloride Hydrate may be used in combination with other antidiabetic agents such as insulin secretagogues, for example sulphonylureas, biguanides, such as metformin, alpha glucosidase inhibitors, such as acarbose, beta agonists, and insulin such as those disclosed in WO98/57649, WO98/57634, WO98/57635 or WO98/57636. The other antidiabetic agents, the amounts thereof and methods of administration are as described in the above mentioned publications. The formulation of the Hydrochloride Hydrate and dosages thereof in said combinations are generally as disclosed for Compound (I) in the above mentioned publications.

In a further aspect the present invention provides the use of Hydrochloride Hydrate for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof Hydrochloride Hydrate may be taken in doses, such as those described in the above mentioned publications

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following examples illustrate the invention but do not limit it in any way.

Preparation of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate

Example 1: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4 g) was suspended in water (25 ml), and concentrated hydrochloric acid (4 ml) was added , forming a clear solution, and then a thick suspension. After 1 hour the suspension was diluted with water (10 ml), the crude product was filtered and then washed with denatured ethanol (20 ml). The crude product was stirred in diethyl ether (50 ml), filtered and dried at 50°C to afford the title compound(3.1 g ,63%).

Example 2: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (4 g) was suspended in denatured ethanol (40 ml), and concentrated hydrochloric acid (4 ml) was added, forming a solution. Water (40 ml) was added, and the resulting suspension was cooled to 0°C and stirred for 3 hours. The product was filtered, washed with acetone (2 x 10 ml) and dried at 50°C to afford the title compound- (3.91 g, 82%).

Example 3: A mixture of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (5.0 g), propan-2-ol (75 ml) and water (20 ml) was stirred and heated to 75°C. Aqueous hydrochloric acid (2.8M, 10 ml) was added and the mixture stirred for 15 minutes at which point a clear solution was observed. After cooling to 25°C seed crystals of rosiglitazone hydrochloride dihydrate were added and the mixture cooled to 0-5°C and stirred for 2 hours. The product was collected by filtration, washed with propan-2-ol (20 ml) and dried under vacuum for 16 hours to give Hydrochloride Hydrate as a white crystalline solid (4.8 g).

CHARACTERISING DATA: The following characterising data were generated for Hydrochloride Hydrate:

A Water content

This was determined as 8.4% w/w using a Karl Fischer apparatus (theory for dihydrate 8.37% w/w).

B Ionic Chlorine

This was determined as 8.5% w/w (theory for dihydrate 8.26% w/w).

C Infrared

The infrared absorption spectrum of a mineral oil dispersion of Hydrochloride Hydrate was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm^{-1} resolution. Data were digitised at 1 cm^{-1} intervals. The spectrum obtained is shown in Figure I. Peak positions are as follows: 3392, 3139, 3094, 2739, 1758, 1751, 1706, 1643, 1632,

1610, 1583, 1545, 1513, 1412, 1357, 1325, 1297, 1265, 1251, 1216, 1179, 1152, 1138, 1110, 1080, 1053, 1033, 1010, 985, 953, 931, 909, 827, 822, 812, 769, 739, 724, 713, 660, 620, 604, 593, 562, 539, 529 and 508 cm^{-1}.

B X-Ray Powder Diffraction (XRPD)

The XRPD pattern of Hydrochloride Hydrate is shown below in Figure II and a summary of the XRPD angles and calculated lattice spacings characteristic of Hydrochloride Hydrate is given in Table I.

A Bruker AXS D8 Advance X-ray powder diffractometer (Cu X-ray source) was used to generate the pattern using the following acquisition conditions:

Tube anode:	Cu
Generator tension:	40 kV
Generator current:	40 mA
Start angle:	2.0 °2θ
End angle:	35.0 °2θ
Step size:	0.02 °2θ
Time per step:	2.5s

Table I.

X-Ray Powder Diffraction Angles and Calculated Lattice Spacing Characteristic of Hydrochloride Hydrate.

Diffraction Angle (°2θ)	Lattice Spacing (Angstroms)
9.1	9.75
12.0	7.37
15.7	5.64
16.3	5.42
18.2	4.88
18.6	4.77
19.8	4.48
20.9	4.24
21.6	4.11
22.8	3.89
24.1	3.69
24.7	3.60
25.4	3.50
26.0	3.42
27.5	3.24
27.7	3.21
28.7	3.11
31.4	2.84
31.6	2.83
32.1	2.79
33.1	2.71
33.6	2.66
34.6	2.59

CLAIMS

1. 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate characterised in that it:

(i) provides an infrared spectrum containing peaks at 3392, 2739, 1751, 1325 and 713 cm^{-1}; and/or

(ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at 9.1, 12.0, 15.7, 16.3 and 19.8 °2θ.

2. A hydrate according to claim 1, which provides an infra red spectrum substantially in accordance with Figure I.

3. A hydrate according to claim 1 or claim 2, which provides an X-ray powder diffraction (XRPD) pattern substantially in accordance with Figure II

4. A hydrate according to any one of claims 1 to 3, in isolated form.

5. A hydrate according to any one of claims 1 to 4, in pure form.

6. A hydrate according to any one of claims 1 to 5, in crystalline form.

7. A process for preparing a hydrate according to claim 1, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound I) is treated with a suitable source of hydrochloride counter-ion and an appropriate amount of water for formation of the Hydrochloride Hydrate; and thereafter the required compound is recovered.

8 A pharmaceutical composition comprising an effective, non-toxic amount of a hydrate according to claim 1 and a pharmaceutically acceptable carrier therefor.

9. A hydrate according to claim 1, for use as an active therapeutic substance.

10. A hydrate according to claim 1, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

11. The use of hydrate for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

12. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of hydrate to a human or non-human mammal in need thereof.

ABSTRACT

5-[4-[2-(N-methyl-N-(2-pyridyl)aminoethoxy]benzyl]thiazolidine-2,4-dione, hydrochloride dihydrate characterised in that it: (I) provides an infrared spectrum containing peaks at 3392, 2739, 1751, 1325 and 713 cm^{-1}; and/or (ii) provides an X-ray powder diffraction (XRPD) pattern containing peaks at 9.1, 12.0, 15.7, 16.3 and 19.8 °2θ; a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

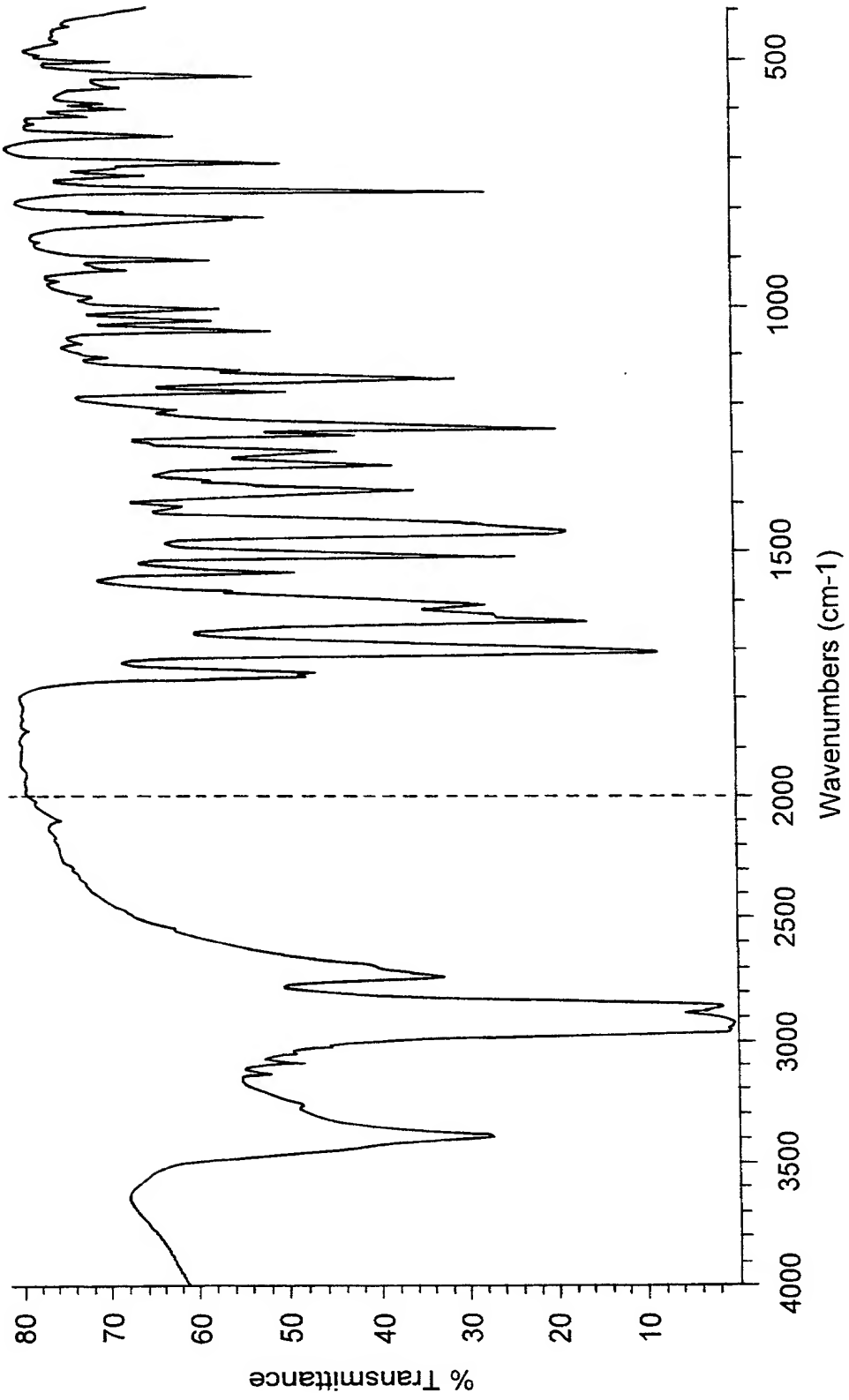
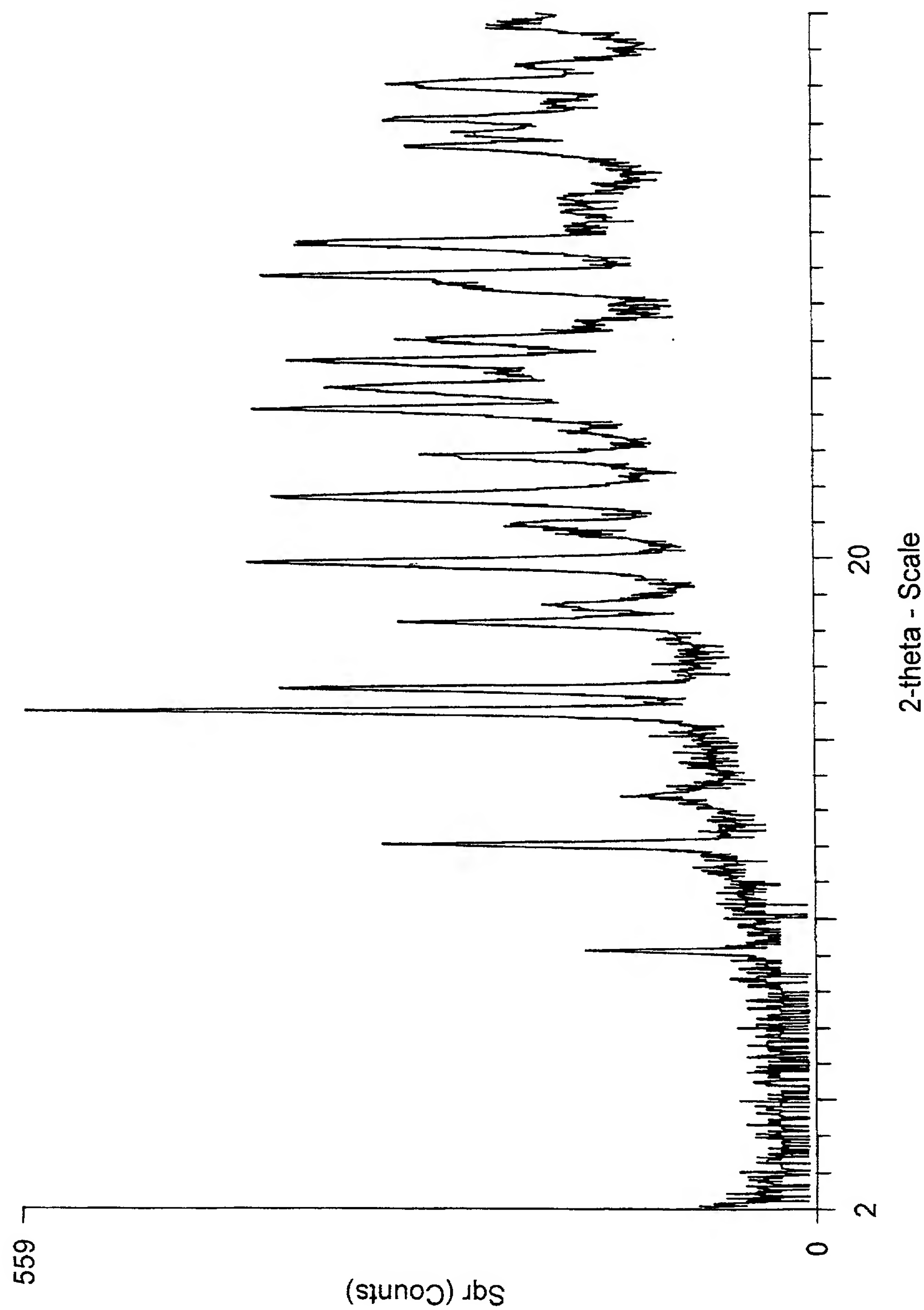


Fig. 1 Infrared Spectrum of Hydrochloride Hydrate.

Fig. 2 X-Ray Powder Diffraction Pattern of Hydrochloride Hydrate



Docket No.: P32286 PCT/GB00/01521

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

THIAZOLIDINEDIONE DERIVATIVE AND ITS USE AS ANTIDIABETIC

the specification of which (check one)
[ ] is attached hereto.
[X] was filed on 19 April 2000 as Serial No. PCT/GB00/01521
and was amended on (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or Inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)

Number	Country	Filing Date	Priority Claimed
9909041.7	GREAT BRITAIN	20 April 1999	Yes

I hereby claim the benefit under Title 35, United States Code, Section 119(e) of any United States provisional application(s) listed below.

Application Number	Filing Date

I hereby claim the benefit under Title 35, United States Code, Section 120 of any United States application(s) or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, Section 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

Serial No.	Filing Date	Status

I hereby appoint the practitioners associated with the Customer Number provided below to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith, and direct that all correspondence be addressed to that Customer Number:

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Address all correspondence and telephone calls to Yuriy Stercho, GlaxoSmithKline, Corporate Intellectual Property-U.S., UW2220, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939, whose telephone number is 610-270-5018.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application ~~or~~ any patent issued thereon.

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